

**REMARKS**

Claims 7, 20, 31, 34-37, 40-49, 54 and 59-66 are pending in the application following entry of this Amendment. The claims have been amended to delete the aspect of the invention relating to nasal administration in favor of the currently preferred ophthalmic administration. Correspondingly, independent composition claims 34, 35, 40 and 41, the only pending independent claims, have been amended to recite a thickening agent consistent with the use of the composition for such use. New claims 59-62 have been added, to recite preferred thickening agents. Support for the use of a thickening agent for ophthalmic administration is supported in the application as filed at least at paragraphs [0044] and [0085]. New claims 63-66 have been added to recite certain preferred cyclodextrins. These claims are supported in the application as filed at least at paragraph [0021]. No new matter has been added by any of the foregoing amendments. Entry of this Amendment is respectfully solicited.

In view of the foregoing amendments, pending claims 7, 34, 35-37, 40-48 and 59-66 relate to compositions adapted for ophthalmic administration comprising fexofenadine or a pharmaceutically acceptable salt thereof, a cyclodextrin or glycofurool excipient to increase the solubility of the fexofenadine, and a thickening agent, with various of these composition claims including other preferred ingredients. Pending dependent claims 20, 31 and 54 relate to methods of treating a patient with the composition of the claim from which they depend by administering an effective amount of the composition to the patient's eye.

The applicants acknowledge the Examiner's withdrawal of the following rejections:

- (i) the rejection of claims 7, 20, 21, 28, 29, 34, 38, 39, 44, 45 and 47, under 35 U.S.C. § 112, second paragraph (Office Action at ¶ 1);
- (ii) the rejection of claims 40 and 49 under 35 U.S.C. § 102(b) based upon U.S. Patent No. 4,254,129 of Carr *et al.* ("Carr") (Office Action at ¶ 2);
- (iii) rejection of claims 40, 41, 49 and 50-57 under 35 U.S.C. § 102(e) based upon U.S. Patent No. 6,103,735 of Aslanian *et al.* ("Aslanian") (Office Action at ¶ 3);
- (iv) the rejection of claims 40, 41 and 49-57 under 35 U.S.C. § 102(e) based upon U.S. Patent No. 6,451,815 of Hwang *et al.* ("Hwang") (Office Action at ¶ 4);
- (v) the rejection of claims 42 and 43 under 35 U.S.C. § 103(a) over Aslanian (Office Action at ¶ 7);

- (vi) the rejection of claims 42 and 43 under 35 U.S.C. § 103(a) over Hwang (Office Action at ¶ 8); and
- (vii) the rejection of claims 41-43 under 35 U.S.C. § 103(a) over Carr (Office Action at ¶ 9);

## **I. Magee (Publication US 2002/0111495 A1) Is Not A Prior Art Reference**

The Examiner has maintained that Magee is prior art to this application. The applicants continue to strenuously object, as it appears that the Examiner is mistaken with respect to the interpretation of when a reference can be accorded the benefit of a filing date earlier than either its publication date (here, August 15, 2002) or earlier than its filing date (here January 31, 2002). Both of Magee's publication and filing dates are too late for Magee to be a prior art reference against the present application, having a perfected foreign priority date of Great Britain Application No. 9822170.8, filed October 13, 1998. *See*, the Declaration and Power of Attorney filed in the present application. Even the U.S. filing date for the present application, April 13, 2001, is before either of the valid effective dates of Magee, mentioned above.

In ¶ 5 of the Detailed Action, the Examiner presents an explanation of the basis for Magee having an earlier filing date – April 4, 1997, the filing date of U.S. Provisional Patent Application No. 60/043,403, of Marfat, et al. (not including Thomas Victor Magee, but including Robert James Chambers, who, with Marfat and Magee are the inventors named in Magee). This provisional application will be referred to hereinafter as “PV '403.” PV '403 thus does not have the same inventive entities as Magee. The Examiner explained that PV '403 gave rise to a PCT application (PCT/IB98/00315, with an international filing date of March 10, 1998, and an international publication date of October 15, 1998), on which national phase U.S. Patent Application 09/308,956 was filed on May 27, 1999, under 35 U.S.C. § 371, and that issued as U.S. Patent 6,380,218 (the '218 Patent). This history cited by the Examiner is accurate, as noted on the cover sheet of the '218 Patent, as is the 35 U.S.C. § 102(e) date of May 29, 1999. After citing this history, the Examiner simply concluded: “Thus, Magee is available as prior art over the instant claims.” Because the Examiner's conclusion is clearly erroneous as a matter of law, the Applicants respectfully but most strenuously traverse all rejections based on Magee. Despite the Examiner's summary of the history of PV '403, neither PV '403 nor the '218 Patent nor

Magee is prior art with respect to the present application. They cannot be used as references to support any prior art rejections of this application.

There are several fundamental flaws in the Examiner's conclusion that Magee is prior art based on PV '403. They are, as explained below: (1) Magee does not and cannot claim PV '403 as a priority application under 35 U.S.C. § 111(b); (2) the earliest possible date that PV '403 became available to the public is the publication date of PCT/IB98/00315, namely October 15, 1998, after the priority date of the present application; (3) Magee specifically states that PV '403 and the '218 Patent do not disclose the subject matter of Magee's invention; and (4) in fact, PV '403 does not provide an enabling disclosure to support the portions of the disclosure of Magee cited by the Examiner and relevant to the rejections of the present application.

**(1) Magee does not and cannot claim PV '403 as a priority application under 35 U.S.C. § 111(b)**

PV '403 and two other provisional applications are listed under "Related U.S. Application Data" on the cover sheet of Magee. Of the three provisional applications, only PV '403 has a filing date predating the priority date of the present application, so even theoretically, only PV '403 of the three could be prior art to the present application. However, it simply is not, legally. Thus, by the very terms of the provisional application statute (35 U.S.C. § 111(b)), PV '403 could become abandoned for priority purposes with respect to Magee, one year from the provisional application filing date, namely, April 4, 1998. Since Magee was not filed until January 31, 2002, it cannot reach back before January 31, 2001 to any provisional application, and certainly not PV '403. Accordingly, for this reason alone, Magee is not prior art based on PV '403.

**(2) PV '403 supports a direct connection to the '218 Patent, not to Magee, and the '218 Patent rightfully is not relied upon as a prior art reference against the present application, since the '218 Patent has a § 102(e) date after the priority date of the present invention**

As explained in section (1) above, PV '403 was abandoned well before the filing date of Magee or any patent application on which it validly relies for a priority filing date. As a result, and assuming only for the sake of argument that PV '403 has an enabling disclosure supporting its asserted progeny resulting in the '218 Patent, the earliest date that PV '403 could be

considered itself to be prior art is the publication date of PCT/IB98/00315, namely October 15, 1998. However, this date is still too late for PV '403 or any of its legitimate progeny to be prior art before the priority date of the present application of October 13, 1998.

**(3) Magee specifically states that PV '403 and '218 do not disclose the subject matter of Magee's invention**

Magee's reference to PV '403 and its progeny (including the applications resulting in the '218 Patent) in paragraph [0001] at page 1 does not claim priority from PV '403. The contrary is true – Magee distinguishes the subject matter of from Magee as follows:

[0001] Reference is made to co-pending International application and U.S. application based thereon, Ser. No. PCT/IB98/00315, both filed Mar. 10, 1998 (Attorney Docket No. PC9762A), and published as WO 98/45268 on Oct. 15, 1998; claiming priority from application Ser. No. 60/043403 filed Apr. 4, 1997 (Attorney Docket No. PC9762), now abandoned; which discloses nicotinamide derivatives having biological activity as inhibitors of PDE4 isozymes, and thus being useful in the treatment of inflammatory, respiratory and allergic diseases and conditions. Nothing that is disclosed in the above-mentioned applications would teach the person of ordinary skill in the pertinent art the novel compounds of the present invention or their unexpectedly high level of inhibitory selectivity for PDE 4 isozymes. [Emphasis added]

Magee's paragraph [0058] is the first paragraph after the heading "DESCRIPTION OF THE STATE OF THE ART." This paragraph states:

[0058] WO 98/45268 (Marfat et al.), published Oct. 15, 1998, discloses nicotinamide derivatives having activity as selective inhibitors of PDE4D isozyme. These selective inhibitors are represented by Formula (0.1.1):  
[STRUCTURE, significantly different from Magee]

The next mention of this international application, based on PV '403 and resulting in the '218 Patent, is in Magee's paragraph [0072]:

[0072] With regard to the disclosures of the above-identified patents and published patent applications, it will

be appreciated that only the disclosure of WO 98/45268 (Marfat et al.) concerns the inhibition of PDE4 isozymes. The state of the art also contains information regarding compounds wholly dissimilar in chemical structure to those of Formula (1.0.0), but which, on the other hand, possess biological activity similar to that of the compounds of Formula (1.0.0). Representative patents and published patent applications disclosing said information are illustrated further below. [Emphasis added]

Magee again refers to these patents or published applications in paragraph [0082] as follows:

[0082] With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that the compounds involved possess the same biological activity as the compounds of Formula (1.0.0). At the same time, however, the artisan will observe that the chemical structures of said compounds disclosed in the prior art are not only diverse from each other but dissimilar to that of the novel compounds of the present invention as well. The state of the art contains still further information regarding compounds which are dissimilar in chemical structure to those of Formula (1.0.0), and which, moreover, do not possess PDE4 inhibitory activity similar to that of the compounds of Formula (1.0.0). Such compounds disclosed in the prior art do, nevertheless, often have therapeutic utility similar to that possessed by the compounds of Formula (1.0.0), i.e., in the treatment of inflammatory, respiratory and allergic diseases and conditions. In particular this is applicable to certain inhibitors of enzymes and antagonists of receptors in the so-called leukotriene pathway. This is especially the case with regard to the leukotrienes LTB<sub>4</sub> and LTD<sub>4</sub>. Accordingly, representative patents and published patent applications disclosing further information of this type are described below. [Emphasis added]

After summarizing several other references, Magee concludes as follows in paragraph [0089]:

[0089] Nothing in the above-described state of the art discloses or would suggest to the artisan the novel

compounds of the present invention or their PDE4 inhibitory activity and the resulting significant improvement in therapeutic index in the treatment of inflammatory, respiratory and allergic diseases and conditions. [Emphasis added]

In view of these statements quoted directly from Magee, it can hardly be said that Magee is claiming priority from PV '403 or its progeny. To the contrary, Magee's inventors are distancing their invention from PV '403 and its progeny. This is another reason that Magee does not and cannot rely on the filing date of PV '403 for a priority date to predate the priority date of the present application.

**(4) PV '403 does not provide an enabling disclosure to support the portions of the disclosure of Magee cited by the Examiner and relevant to the rejections of the present application**

Enclosed is a certified copy of U.S. Provisional Patent Application No. 60/043,403, filed April 4, 1997, by Marfat et al. (not including Thomas Victor Magee, but including Robert James Chambers, who, with Marfat and Magee are the inventors named in Magee). This provisional application will be referred to hereinafter as "PV '403." A review of PV '403 clearly indicates that this provisional application does not support the disclosures of Magee relied upon by the Examiner, except perhaps for its disclosure of a different PDE4 inhibitory active ingredient than the PDE4 active ingredient disclosed in Magee.

While PV '403 discloses use of the active ingredient to treat a number of diseases and conditions (see pages 13-14), including allergic rhinitis, it uses an active ingredient that is different from both Magee and from fexofenadine of the present application. PV '403 does not disclose any combination with any ingredients suitable for nasal or ophthalmic administration, and does not come close to disclosing anything like the large laundry list of disconnected ingredients in Magee. The closest PV '403 comes to a disclosure of administration of the PDE4 inhibitory active ingredient in a way even remotely arguably relevant, yet dissimilar to the administration in the present invention or the portions of Magee relied upon by the Examiner is at page 51, lines 21-23, which recites:

Additionally, the active compounds may be administered topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

PV '403 does not disclose fexofenadine, any type of cyclodextrin or glycofufrol or other ingredient that increases solubility of fexofenadine, a poloxamer, propylene glycol, or the ophthalmic route of administration relied upon by the Examiner in the Examiner's use of Magee in the prior art rejections of the present application. Nor does PV '403 disclose any thickening agent now claimed in the present application. PV '403 simply does not support Magee's disclosure relied upon by the Examiner, and does not disclose any relevant information to render the presently claimed invention unpatentable, even assuming only for the sake of argument that PV '403 is a viable prior art reference, which it clearly is not.

PV '403's lack of any enabling disclosure supporting Magee's asserted disclosure is another reason that Magee itself is not prior art under 35 U.S.C. § 102(e).

**(5) Magee must be withdrawn as a prior art reference**

In view of the above, it appears that, at best, Magee has an effective filing date of January 31, 2001, the filing date of Provisional application No. 60/265,240, even assuming only for the sake of argument that that application contains an enabling disclosure for Magee. January 31, 2001 is not sufficiently early to qualify Magee as prior art against the present application, which is entitled to a filing date of October 13, 1998. Therefore, the prior art rejections based in whole or in part on Magee are improper, and reconsideration and withdrawal of the rejections are respectfully requested.

**II. Rejections under 35 U.S.C. § 103(a) Based Upon Carr or Hwang.**

Carr and Hwang are relied upon, each in combination with Magee, to support rejections based on the asserted obviousness of the present invention. The Examiner recognized that neither Carr nor Hwang themselves could support such rejections, as they are missing disclosures or even suggestions concerning ingredients claimed in the claims of the present application. Since Magee cannot be relied upon to supply the missing ingredients, as it is not proper prior art as established above, the rejections based on Carr or Hwang in combination with Hwang must fall. Reconsideration and withdrawal of these rejections are respectfully solicited.

## CONCLUSION

In view of the foregoing, it is submitted that all pending claims are in a condition for allowance. Reconsideration, withdrawal of the rejections, and issuance of the claims at the earliest opportunity are respectfully requested.

Respectfully submitted,

*August 15, 2005* **Lisbeth Illum, et al.**  
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Enclosures:

Certified Copy of U.S. Provisional Patent Application No. 043,403, filed April 4, 1997;  
Petition for 2-Month Extension of Time